Journal of the American Heart Association

ORIGINAL RESEARCH

Favorable Atrial Remodeling After Percutaneous Pulmonary Valve Implantation and Its Association With Changes in Exercise Capacity and Right Ventricular Function

Heiner Latus, MD; Danik Born, MD; Nerejda Shehu, MD; Heiko Stern, MD; Alfred Hager, MD; Stainimir Georgiev, MD; Daniel Tanase, MD; Christian Meierhofer, MD; Peter Ewert, MD; Andreas Eicken, MD; Oktay Tutarel, MD

BACKGROUND: Right atrial (RA) dilatation and impaired right ventricular (RV) filling are common in patients with RV outflow tract dysfunction. We aimed to study potential correlations between atrial function with clinically relevant hemodynamic parameters and to assess the predictive impact of atrial performance on the recovery of exercise capacity and RV pump function after percutaneous pulmonary valve implantation (PPVI).

METHODS AND RESULTS: Altogether, 105 patients with right ventricular outflow tract dysfunction (median age at PPVI, 19.2 years; range, 6.2–53.4 years) who underwent cardiac magnetic resonance imaging before and 6 months after PPVI were included. RA and left atrial maximal and minimal volumes as well as atrial passive and active emptying function were assessed from axial cine slices. RA emptying function was inversely related to invasive RV end-diastolic pressure, and RA passive emptying correlated significantly with peak oxygen uptake. After PPVI, a significant decrease in RA minimum volume was observed, whereas RA passive emptying function improved, and RA active emptying function decreased significantly. Patients with predominant right ventricular outflow tract stenosis showed more favorable changes in RA active and left atrial passive emptying than those with primary volume overload. None of the RA and left atrial emptying parameters was predictive for recovery of peak oxygen uptake or RV ejection fraction.

CONCLUSIONS: In patients with right ventricular outflow tract dysfunction, impaired RA emptying assessed by cardiac magnetic resonance imaging was associated with increased RV filling pressures and lower exercise capacity. PPVI leads to a reduction in RA size and improved passive RA emptying function. However, RA function was not associated with improved exercise performance and RV pump function.

Key Words: atrial dysfunction ■ diastolic ventricular function ■ percutaneous pulmonary valve implantation

Right ventricular outflow tract (RVOT) dysfunction is commonly encountered in patients after surgery of conotruncal congenital heart defects such as tetralogy of Fallot (TOF) or pulmonary atresia and can also be present after implantation of bioprosthetic valves or homografts in the pulmonary position. If left untreated, patients with a dysfunctional RVOT are at increased risk for heart failure, arrhythmia, and sudden cardiac death.[1] As a consequence of long-term right ventricular (RV) pressure and/or volume overload, unfavorable changes in right atrial (RA) dimension and function frequently evolve and are associated with RV

Correspondence to: Heiner Latus, MD, Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Centre Munich, Technical University of Munich, Lazarettstr. 36, 80636 Munich, Germany. E-mail: heiner.latus@googlemail.com

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In patients with right-sided congenital heart disease, parameters of right atrial emptying show significant associations with peak oxygen uptake and invasive filling pressures before percutaneous pulmonary valve implantation.
- After percutaneous pulmonary valve implantation, right atrial emptying function improved, but was not predictive for an improvement in exercise capacity or right ventricular function.

What Are the Clinical Implications?

- Noninvasive quantification of atrial emptying function by cardiac magnetic resonance imaging may represent a useful adjunct to assess hemodynamics before percutaneous pulmonary valve implantation.
- Its implications for defining the best time point for percutaneous pulmonary valve implantation still needs to be defined.

Nonstandard Abbreviations and Acronyms

PPVI	percutaneous pulmonary valve implantation
PR	pulmonary regurgitation
RA	right atrial
TOF	tetralogy of Fallot
TR	tricuspid valve regurgitation

systolic dysfunction, restrictive RV filling, exercise intolerance, and adverse outcome.[2,3] Importantly, atrial size and emptying characteristics are closely related to diastolic ventricular filling properties that can be quantified noninvasively using cardiac magnetic resonance (CMR) imaging.[4]

By reducing RV overload, percutaneous pulmonary valve implantation (PPVI) can preserve biventricular function and prevent these long-term changes. However, although PPVI is nowadays performed with an overall high procedural success rate, an improvement in exercise performance and RV function after restoration of pulmonary valve function is not observed in all patients.[5] Additionally, restrictive RV filling has been described as an important hemodynamic burden among patients with dysfunctional RVOT,[4,6] but the effect of PPVI on restrictive RV filling and its impact on clinical status and hemodynamics remain largely unknown. Consequently, there still remain uncertainties about the indication and optimal timing of PPVI in this population.

By using CMR imaging, our study aimed to analyze biatrial volume and emptying function in patients with RVOT dysfunction to reveal its association with invasive hemodynamic data, exercise capacity, and the severity of tricuspid valve regurgitation (TR). Furthermore, biatrial remodeling following PPVI and the predictive impact of atrial performance on the recovery of exercise capacity and RV pump function after PPVI is assessed.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

Patients who underwent PPVI at the German Heart Center, Munich between September 2006 and January 2017 were considered for inclusion in this retrospective analysis of prospectively collected data (Figure 1). Patients who are referred for PPVI at our center are usually evaluated according to a standardized protocol including the following: history with assessment of New York Heart Association functional class, echocardiography, CMR imaging, and cardiopulmonary exercise testing before and 6 months after PPVI as previously reported.[7,8] The primary outcome was improved exercise capacity after PPVI measured by peak oxygen

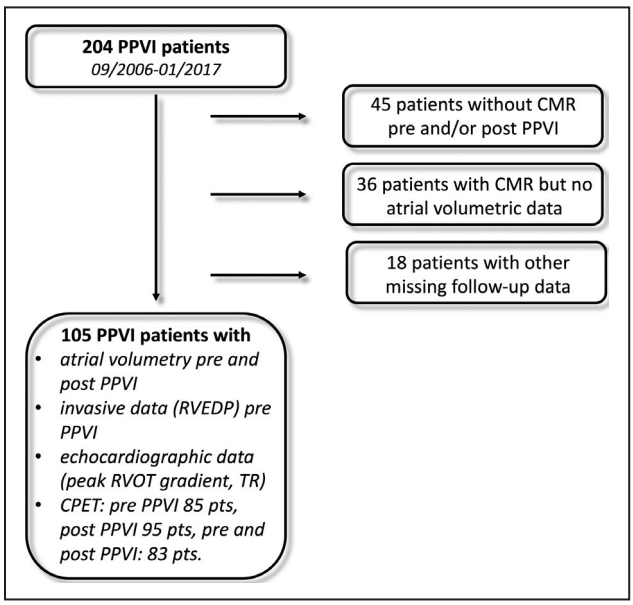

Figure 1. Graph displaying the study flow with the total number of patients with PPVI at our center and the number of patients included for final analysis.
CMR indicates cardiac magnetic resonance; CPET, cardiopulmonary exercise testing; PPVI indicates percutaneous pulmonary valve implantation; RVEDP, right ventricular end-diastolic pressure; and RVOT, right ventricular outflow tract.

uptake (VO_2) and improved right ventricular ejection fraction (RVEF) after PPVI. The relation between atrial volume and function at baseline as well as after PPVI with the primary outcome measures were studied.

This study complies with the Declaration of Helsinki, and the ethics committee of the Medical Faculty of the Technical University of Munich has approved the research protocol. All patients or parents of the patients gave written informed consent.

CMR Imaging

CMR imaging studies were acquired on a 1.5 T system (Magnetom Avanto; Siemens, Erlangen, Germany) with a standard 12-element cardiac phased array coil and with patients in a supine position. We used a standard, balanced, steady-state free precession sequence (TrueFisp; Siemens) with retrospective ECG gating and a slice thickness of 5, 6, or 8 mm depending on bodyweight, no interslice gap, repetition time/echo time=40/1.3 ms, field of view=340×276, acquisition matrix=192×192, voxel size=1.78×1.44×5–8 mm, and 25 reconstructed phases per R-R interval acquired during breath holds in adults and during free breathing in young children.

End-diastolic volume, end-systolic volume, stroke volume, and ejection fraction for the right ventricle and left ventricle were calculated from axial cine data sets after endocardial borders were traced manually. Standard 2-dimensional phase contrast flows in the proximal main pulmonary artery were measured, and pulmonary regurgitant fraction was calculated.

CMR Image Analysis of Atrial Size and Function

The endocardial contours of the right atrium and left atrium were manually traced in every slice of the stack of axial cine images. The atrial appendages were included in the measurement of atrial volumes, whereas the superior and inferior caval vein, coronary sinus, and pulmonary veins were excluded at their junction to the atrium (Figure 2A).[9] Atrial volumes over time were obtained by adding all the atrial areas of all slices for all cardiac phases by the summation disk method (Figure 2A). All parameters were adjusted to body surface area that was calculated using the Mosteller method.

Atrial Physiology and Parameters of Biatrial Size and Function

The role of the atria during the cardiac cycle can be divided into 3 different phases. During ventricular systole (phase 1), the atria serve as a reservoir for venous blood return. During early diastole (phase 2), the atria act as passive conduits by relaxation of the ventricle. In late diastole (phase 3), ventricular filling is augmented by an active atrial contraction (atrial kick or booster function) (Figure 2B). Accordingly, the following atrial volumes were assessed: maximal atrial volume at (ventricular) end-systole, minimal atrial volume at (ventricular) end-diastole, as well as minimal and maximal atrial volume at mid-diastole.

Cyclic volume change was quantified by subtraction of minimal from maximal atrial volume. Passive emptying volume was calculated by subtracting minimal atrial volume at mid-diastole from maximal atrial volume. Active emptying volume was calculated by subtracting minimal atrial volume at (ventricular) end-diastole from maximal atrial volume at mid-diastole (before atrial contraction). Passive emptying function was calculated as passive emptying volume divided by maximal atrial volume, and active emptying function was calculated as active emptying volume divided by atrial volume at mid-diastole (both expressed as percentage).[10] E/A ratio was defined as passive emptying volume divided by active emptying volume.

Echocardiography

Transthoracic echocardiography (Vivid 7; General Electric, Vingmed, Horten, Norway) was performed to determine the maximal velocity across the RVOT using continuous wave Doppler. RVOT gradients were calculated according to the Bernoulli equation. The severity of TR was graded according to current guidelines and was quantified as no/mild, moderate, and severe.[11]

Cardiopulmonary Exercise Testing

All patients underwent symptom-limited cardiopulmonary exercise testing in an upright position on a bicycle ergometer as previously described.[7] Peak VO_2 was chosen as a correlate for maximal exercise capacity.

Statistical Analysis

All continuous variables were tested for normal distribution using the D'Agostino-Pearson test and are presented as mean with SD or median and range, as appropriate. Comparisons between the subgroups were made with the Student *t* test, the Mann-Whitney *U* test, or the Fisher exact test, as appropriate. Pearson correlation coefficient was used to analyze simple linear relationships between different variables. Binary logistic regression analysis was used to assess predictors for the following proposed outcome measures: (1) improved exercise capacity after PPVI and (2) improved RVEF after PPVI (odds ratio [OR] with 95% CI). Analysis was performed using GraphPad (San Diego, CA) and SPSS statistical software package (version 25.0; IBM, Armonk, NY). A P value <0.05 was considered statistically significant.

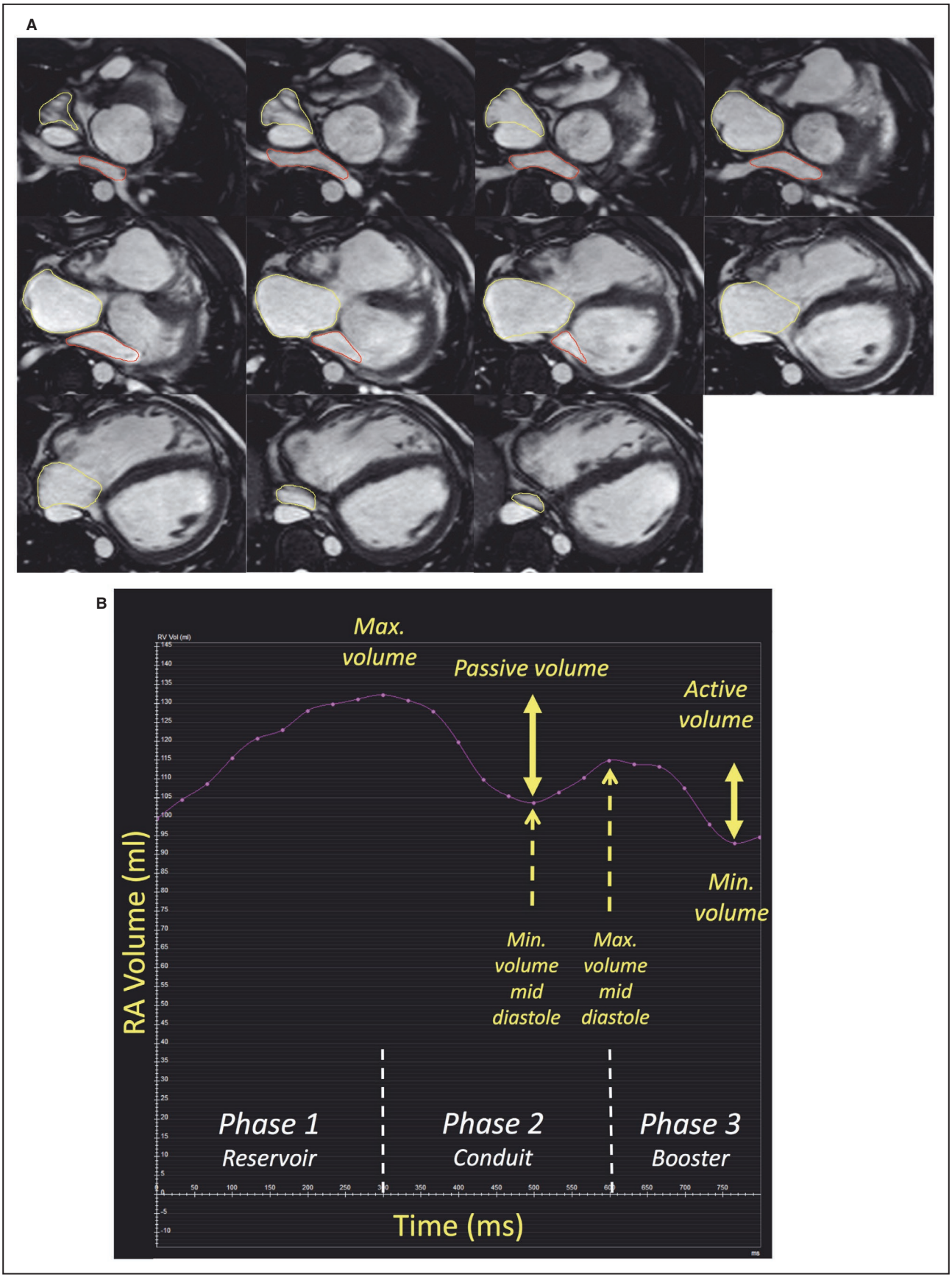
A
B
RV Vol (ml)
Max. volume
Passive volume
Active volume
Min. volume
Min. volume mid diastole
Max. volume mid diastole
RA Volume (ml)
Phase 1 Reservoir
Phase 2 Conduit
Phase 3 Booster
Time (ms)

Figure 2. Assessment of biatrial volumes and parameters of atrial emptying by manual segmentation of the right atrium (RA, yellow) and left atrium (red) through a stack of axial slices covering both atria and ventricles in 1 cardiac cycle (25 phases) (A) and representative time vs volume curve of the RA with its characteristic biphasic shape and the corresponding measures of RA maximum (Max.) volume, RA minimum (Min.) volume, passive emptying volume, and active emptying volume (B).
Atrial passive emptying function was calculated as passive emptying volume divided by maximal atrial volume, and active emptying function was calculated as active emptying volume divided by maximal atrial volume at mid-diastole (both expressed as percent).

RESULTS

Patient Characteristics and Clinical Data

For the intended analysis of our study, patients had to be excluded because of lack of appropriate CMR imaging data or missing follow-up data. For detailed information on the selection of the study population, please see Figure 1. Altogether, 105 patients were included (37 women [35%]; median age at PPVI, 19.2 years; interquartile range, 6.2–53.4 years; Table 1). The follow-up was performed 6.4±1.8 months after PPVI. The most common underlying congenital heart disease were TOF/pulmonary atresia with ventricular sepal defect (53%), common arterial trunk (22%), and patients after pulmonary autograft (Ross) procedure (12%). The majority of patients (62%) had primary RVOT stenosis (defined as peak RVOT gradient ≥50 mm Hg and pulmonary regurgitation (PR) <20%), 26% of the patients had predominant PR (PR ≥20%), and 12% of the patients had RV volume/pressure load in combination with other factors such as declining peak VO_2 and/or impaired RVEF that resulted in the indication for PPVI.

Both New York Hearth Association functional class (P<0.001) and exercise capacity (P=0.0009) improved significantly after PPVI. The echocardiographic peak gradient across the RVOT was 68±21 mm Hg before PPVI and decreased significantly to 28±10 mm Hg (P<0.0001) after PPVI. Heart rate during the CMR imaging studies did not change significantly (57±12 to 73±11 per minute, P=0.24). In 83 of the 105 patients, cardiopulmonary exercise testing data were available before and after PPVI, and peak VO_2 increased significantly from 28.9±8.2 to 30.8±8.8, P<0.001 (peak VO_2 predicted from 74±17 to 80±16, P<0.001).

Table 1. Baseline Characteristics of the Study Population

Variable	Value
Men/women	68/37
Diagnosis	
Tetralogy of Fallot/pulmonary atresia with ventricular septal defect	56 (53)
Common arterial trunk	23 (22)
Ross (pulmonary autograft) procedure	11 (12)
Pulmonary atresia with intact ventricular septum	5 (5)
Rastelli procedure	4 (4)
Complete atrioventricular septal defect	4 (4)
Valvular pulmonary stenosis	2 (2)
Age at PPVI, y	19.2 (6.2–53.4)
Weight, kg	61±23
Height, cm	162±19
BSA, m^2	1.64±0.40

Data are presented as number, mean±SD, median (range), or number (percent). BSA indicates body surface area (Mosteller method); and PPVI, percutaneous pulmonary valve implantation.

CMR Imaging Findings of Biatrial Size and Emptying Function

After PPVI, there was a significant decrease in minimal RA volume at (ventricular) end-diastole (RA_{min}) (38±17 to 33±15 mL/m^2; P<0.0001) and maximal right atrial volume at (ventricular) end-systole volumes (58±21 to 52±20 mL/m^2; P<0.0001; Table 2). RA passive emptying function improved significantly (19%±6% to 22%±6%; P<0.0001), whereas RA active emptying function decreased significantly (33%±14% to 32%±10%; P=0.005). RA E/A ratio increased from 1.0±0.4 to 1.2±0.5 (P<0.001). Maximal left atrial volume at (ventricular) end-systole volume increased (36±10 to 38±10 mL/m^2; P=0.001) and minimal left atrial volume at (ventricular) end-diastole volume remained unchanged (19±7 to 19±6 mL/m^2; P=0.09). Left atrial (LA) passive emptying function improved (31%±7% to 33%±8%; P<0.001) significantly, whereas LA active emptying function (43%±135% to 42%±11%; P=0.79) did not change. LA E/A ratio increased from 1.5±0.7 to 1.6±0.6 (P=0.005).

Associations of RA and LA Volumes and Function

RA passive emptying function (r=−0.27, P=0.02) and baseline RA active emptying function (r=−0.35, P=0.001) before PPVI showed significant inverse relationships with invasive RV end-diastolic pressures measured at the time of PPVI (Figure 3), whereas RA_{min} volume was not significantly related with RV end-diastolic pressures (r=0.15, P=0.13).

Both RA passive emptying function (r=0.23, P=0.04) and LA passive emptying function (r=0.26, P=0.02) were significantly related to peak VO_2 before PPVI (Figure 4). No significant associations between these variables were observed after PPVI.

RA_{min} and RA emptying function showed no significant relationships with the peak RVOT gradient or the degree of PR before PPVI.

Changes in RA size and emptying function were also not related to the decrease in peak RVOT gradient.

Table 2. Changes in Clinical, Echocardiographic, and Cardiac Magnetic Resonance Data Following PPVI

Variable	Before PPVI	After PPVI	*P* value
NYHA class I/II/III/IV	28/69/8/0	85/18/2/0	<0.001*
Peak VO_2, mL/kg per min	28.9±8.2	30.8±8.8	<0.0001*
Peak VO_2 predicted, %	74±17	80±16	<0.0001*
TR, mild/moderate/severe	56/22/27	73/27/5	<0.001*
Heart rate, per min	75±12	73±11	0.24
RVOT gradient echo, mm Hg	68±21	28±10	<0.0001*
PR, %	9 (0–55)	1 (0–33)	<0.0001*
RVEDVi, mL/m^2	91±27	82±25	<0.0001*
RVESVi, mL/m^2	43±25	37±21	<0.0001*
RVSVi, mL/m^2	48±13	46±10	0.17
RVEF, %	54±13	57±10	0.0008*
LVEDVi, mL/m^2	73±16	81±17	<0.0001*
LVESVi, mL/m^2	32±10	34±10	0.0004*
LVSVi, mL/m^2	42±10	47±10	<0.0001*
LVEF, %	57±9	58±7	0.25
Cardiac index, L/min per m^2	3.1±0.8	3.4±0.8	0.0008*
RA_{max} i, mL/m^2	58±19	52±17	<0.0001*
RA_{min} i, mL/m^2	37±15	33±13	<0.0001*
RA cyclic volume change, mL/m^2	20±7	19±6	<0.0001*
RA passive emptying function, %	19±6	22±6	<0.0001*
RA active emptying function, %	25±7	23±6	0.01*
RA E/A	1.0±0.4	1.2±0.5	<0.001*
LA_{max}i, mL/m^2	36±10	39±9	0.0003*
LA_{min}i, mL/m^2	19±7	20±6	0.15
LA cyclic volume change	17±5	19±5	<0.0001*
LA passive emptying function, %	31±6	32±8	0.009*
LA active emptying function, %	29±6	30±5	0.90
LA E/A	1.5±0.7	1.6±0.6	0.005*

Data are presented as number, mean±SD, or median (range). EDV indicates end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; i, indexed; LA, left atrial; LV, left ventricular; NYHA, New York Heart Association; PR, pulmonary regurgitant fraction; RA, right atrial; RV, right ventricular; RVOT, right ventricular outflow tract; SV, stroke volume; TR, tricuspid valve regurgitation; and VO_2, oxygen uptake.

*P<0.05.

Absolute decreases in PR showed a weak relationship with changes in RA_{min} (r=0.21, P=0.03), whereas parameters of RA emptying were unrelated to the change in PR.

Role of TR

Before PPVI, TR was absent or mild in 56 patients (53%), moderate in 22 patients (21%), and severe in 27 patients (26%). Following PPVI, TR severity decreased significantly (P<0.001) within the total study population (Table 2). In all TR subgroups, RA_{min} volume decreased significantly after PPVI (Figure 5). Compared with patients with no/mild TR, patients with severe TR had larger RA_{min} volumes (P=0.017) before PPVI that remained significantly increased after PPVI (P=0.03), although the absolute reduction in RA_{min} volume was more pronounced in these patients (Figure 6). No significant differences before and after PPVI were observed in RA passive emptying function between the TR groups, and only in patients with severe TR, RA passive emptying improved significantly. RA active emptying function was significantly lower in the group with severe TR compared with the group with no/mild TR both before and after PPVI.

Impact of RV Pressure and Volume Load

Patients with predominant RV volume overload (PR >20%, n=27) were compared with a group of patients with isolated pressure overload (peak RVOT gradient >50 mm Hg, PR <20%, n=27). The groups were matched with regard to age (22.6±10.4 versus 22.1±9.6 years; P=0.95), underlying diagnoses, and sex. No differences in clinical parameters (New York Heart Association functional class, peak VO_2) and TR severity were observed between the 2 groups. Patients with predominant PR showed significantly higher indexed right ventricular end-diastolic

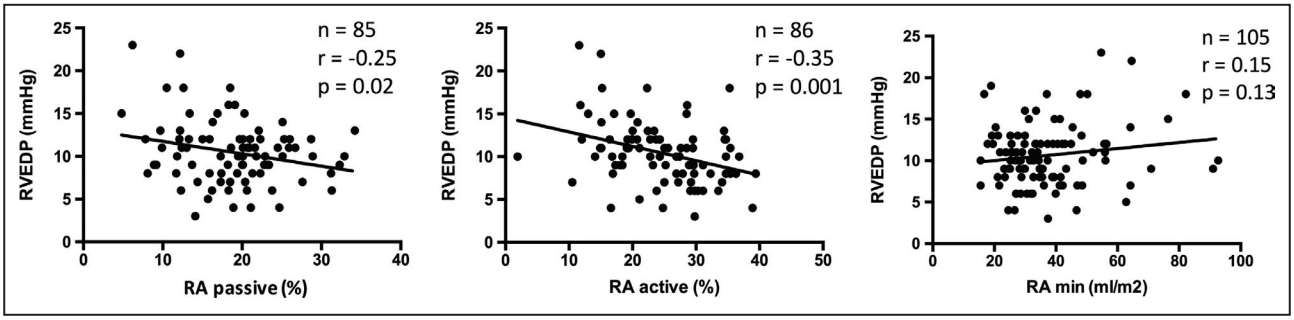

Figure 3. **Right atrial (RA) passive and active emptying function showed an inverse correlation with invasively assessed right ventricular end-diastolic pressure (RVEDP), whereas RA minimum (min) volumes were not significantly related with RVEDP.**

volumes (RVEDVi) before PPVI (100±30 versus 83±30 mL/m^2, *P*=0.004), whereas RVEF (55%±14% versus 56%±4%, *P*=0.47) and left ventricular parameters were similar. Indices of biatrial size and emptying function did not differ between the 2 groups before PPVI (Figure 7). Following PPVI, RA_{min} volumes decreased, and RA passive emptying function increased significantly in both groups. Although RA active emptying function remained unchanged in the stenosis group (*P*=0.44), a significant decrease (*P*=0.001) was noted in patients with PR. Although not different before PPVI (*P*=0.19), LA passive emptying function improved significantly in patients with isolated pressure overload (*P*=0.002) but remained unchanged in the PR group (*P*=0.99).

Predictors for Improved Exercise Capacity and Improved RVEF After PPVI

Of the 83 patients who had a before and after PPVI cardiopulmonary exercise testing study, 59 patients (71%) showed an improvement in peak VO_2 (defined as an increase in peak VO_2 predicted following PPVI). In a binary logistic regression model, significant predictors for an increase in peak VO_2 were lower peak VO_2 (OR, 0.97; 95% CI, 0.93–0.99; *P*=0.01), a lower baseline RVOT gradient (OR, 0.97; 95% CI, 0.94–0.99; *P*=0.01) and the absolute change in RVOT gradient (OR, 0.97; 95% CI, 0.94–0.99; *P*=0.007; Table 3).

In 65 of the 105 patients (62%), an improvement in RVEF was observed after PPVI. An increase in RVEF was associated with New York Heart Association class >I (OR, 2.90; 95% CI, 1.06–7.95; *P*=0.039), higher indexed right ventricular end-systolic volumes (RVESVi) (OR, 1.05; 95% CI, 1.02–1.08; *P*=0.002), lower RVSVi (OR, 0.94; 95% CI, 0.90–0.97; *P*=0.001) as well as lower RVEF (OR, 0.88; 95% CI, 0.83–0.93; *P*=0.0001) and left ventricular ejection fraction (OR, 0.95; 95% CI, 0.90–1.00; *P*=0.036; Table 4).

Neither invasively assessed right ventricular end-diastolic pressure before PPVI nor biatrial volumes and parameters of passive and active emptying were found to be predictive for both outcome measures.

DISCUSSION

Our study demonstrated that in patients with RVOT dysfunction, parameters of RA passive and active emptying function derived from CMR imaging atrial volumetry correlated inversely with invasive RV end-diastolic pressures. Furthermore, both impaired RA and LA emptying function were associated with reduced exercise capacity. Following PPVI, a significant decrease in RA volumes and significant changes in passive and active RA

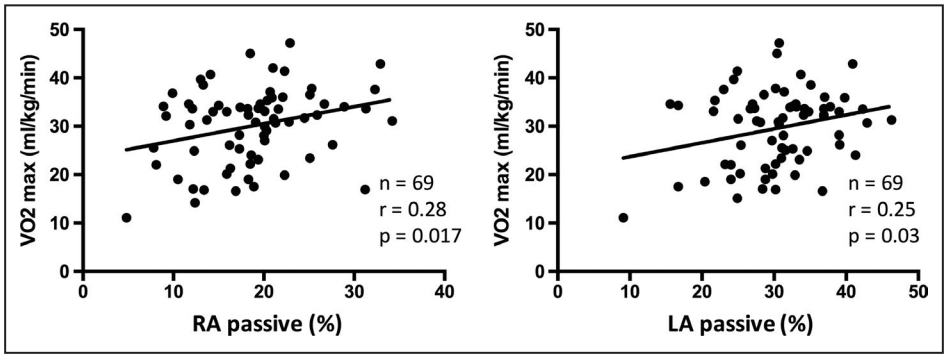

Figure 4. **Significant correlations were found between both right atrial (RA) and left atrial (LA) passive emptying function and maximal (max) oxygen uptake (VO_2).**

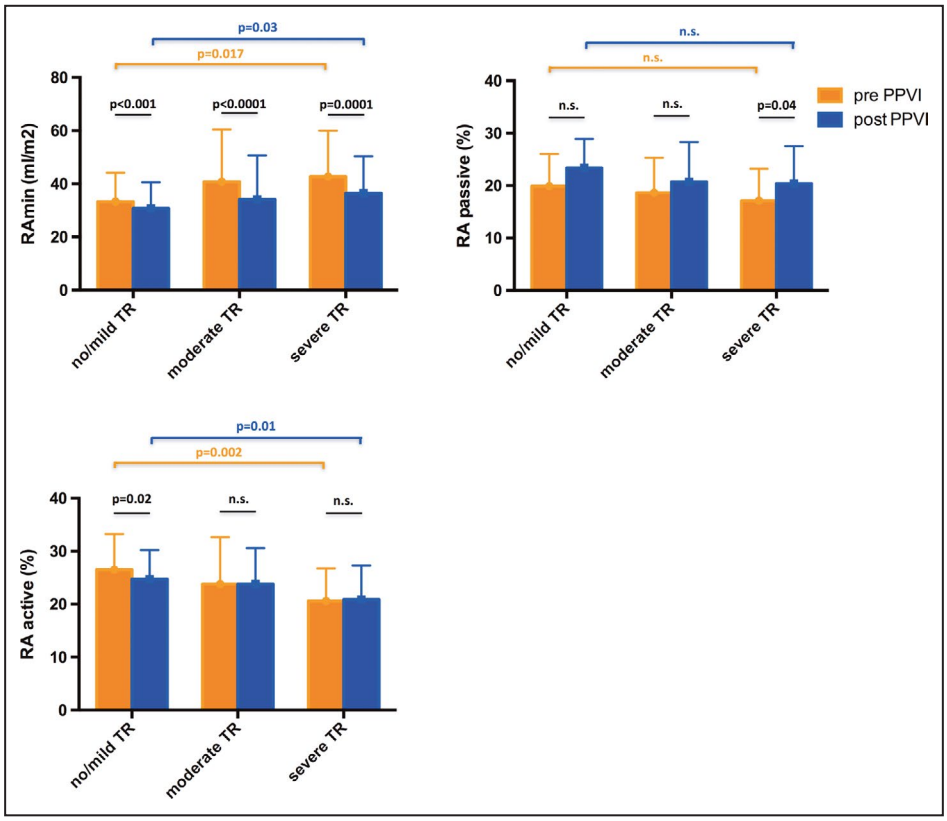

Figure 5. Graphs displaying changes of right atrial minimal (RAmin) volume and right atrial (RA) passive and active emptying function before (orange) and after (blue) percutaneous pulmonary valve implantation (PPVI) according to the severity of tricuspid valve regurgitation (TR) before valve implantation.
Data are presented as mean with 1 SD. n.s. indicates not significant.

emptying were observed. Compared with patients with predominant volume overload, those with primary pressure overload showed a more favorable RA remodeling pattern for RA active and LA passive emptying. Neither RA size nor passive or active emptying parameters were able to predict an improvement in exercise performance or RVEF during short-term follow-up after PPVI. Therefore, our results suggest that RV filling characteristics play an important hemodynamic role in patients with RVOT dysfunction but may not help to predict a short-term improvement after PPVI.

Role of RA Dimension and Emptying Function in Patients With RVOT Dysfunction

In patients with repaired TOF and varying degrees of RV pressure and/or volume overload, restrictive RV filling and abnormal early relaxation are well described.[12,13] However, identification of impaired RV diastolic function using noninvasive imaging techniques is challenging.[14] Restrictive RV physiology defined by pulmonary arterial end-diastolic forward flow has initially been linked with a preserved hemodynamic state, but other studies were not able to confirm the reliability and clinical usefulness of this marker.[12] Considering the close relationship between atrial emptying and ventricular filling, parameters of atrial emptying derived by echocardiography and CMR imaging have been used to characterize diastolic function of the right ventricle and left ventricle.[9,10,15] Our results support these findings by demonstrating a significant relationship of passive and active RA emptying function with invasively measured end-diastolic RV pressures. In contrast, RA volumes, which are frequently used in clinical routine as a sign of RV restriction, were not related to invasive pressures, probably because of a varying amount of coexisting TR. The clinical relevance of impaired early RV filling in this population is further supported by the observed relationship between impaired RA passive emptying function and reduced exercise capacity and is in accordance with previous studies.[9]

Changes in Atrial Size and Emptying Function in Response to PPVI

Accompanied by a reduction in RV dimensions and improved RV pump function, a significant decrease in

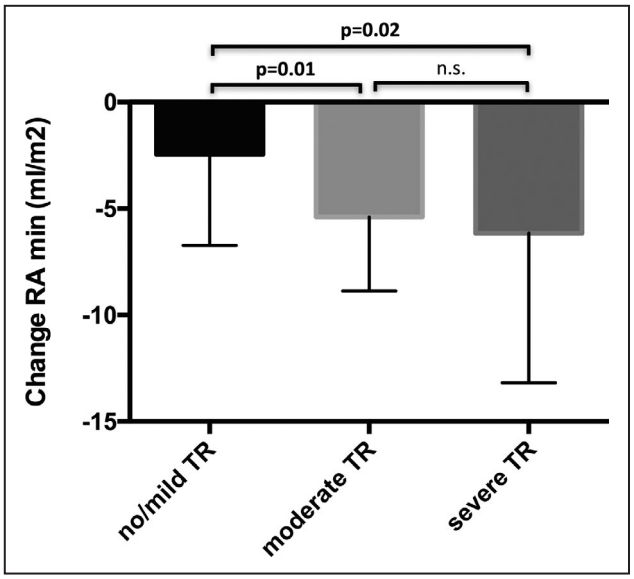

Figure 6. Diagram displaying the absolute change in right atrial minimal volume (RAmin) after percutaneous pulmonary valve implantation (PPVI).
Patients with severe tricuspid valve regurgitation (TR) before PPVI showed the most distinct reduction in RAmin. Data are presented as mean with 1 SD. n.s. indicates not significant.

RA size was also observed in our study, which is consistent with other studies that quantified atrial dimensions using CMR imaging.[16] Given that RA dilatation is associated with the occurrence of supraventricular tachycardia and represents an independent predictor for adverse clinical events in this population,[2,3,17] the reduction in RA size after PPVI constitutes a beneficial adjunct to the favorable ventricular remodeling process. Furthermore, a recent study on patients with TOF demonstrated that increased RA volume was a significant predictor for an adverse outcome after surgical pulmonary valve replacement.[18]

The improvement in RA passive emptying function and the decrease in active emptying after PPVI certainly indicates better early filling of the right ventricle. These findings illustrate the complex response of RV filling that occurs with unloading of the right ventricle and might explain why previous studies reported contrary results with either improved or unchanged diastolic ventricular function after PPVI.[19–22] A potential explanation for these divergent findings could be the use of different echocardiographic and CMR imaging techniques to assess diastolic function such as tricuspid valve inflow analysis, tissue Doppler, or strain imaging. Time of follow-up after PPVI could also lead to different results, because improvement in RV diastolic function seems to be delayed compared with recovery of systolic performance.[19] Therefore, uncertainties about the impact of PPVI on intrinsic RV diastolic function remain, because all of these studies primarily assessed load-dependent measures of ventricular filling.

Role of TR

Additional volume overload attributable to significant TR is common in patients with RVOT dysfunction. Previous studies reported a beneficial effect of volume unloading by PVR on tricuspid valve function even without concomitant tricuspid valve surgery repair.[23,24] We were able to confirm these observations and further demonstrated that patients with moderate and severe TR also responded to PPVI with a greater reduction in RA volumes. Nevertheless, RA size still remained enlarged, and impaired active emptying function was present in patients with severe TR before and after PPVI. Accordingly, our results suggest that patients with relevant TR benefit considerably from PPVI with regard to reduction in RA size, but RA dilatation and impaired emptying persist after valve restoration at least at short-term follow-up, which might become of prognostic relevance in the long-term.[8]

Impact of RV Pressure and Volume Load

It has been hypothesized that the response to PPVI differs between pressure and volume- loaded right ventricles. In the study by Lurz and colleagues, RVEF recovered only in patients with primary stenosis, whereas it remained unchanged in patients with primary PR.[25] Another study found a significant increase in RV strain after PPVI solely in the group with predominant stenosis, whereas left ventricular strain improved significantly in both groups.[26] By using a matched subgroup analysis, our study adds to these findings that changes in RA active and LA passive emptying function were more favorable in the group with isolated stenosis, whereas RA dimensions decreased to the same extent in both groups. Accordingly, recovery of atrial emptying function seems to be impaired in patients with enlarged right ventricles, although volume overload could be effectively reduced by PPVI. Whether this feature is associated with long-term ventricular remodeling, maintenance of exercise capacity, and prognosis in this group needs to determined in future studies. It is important to note that RA dimensions and TR severity did not differ between the 2 groups, whereas patients with primary RV volume overload showed larger RV end-diastolic volumes. We can only speculate about this finding, but reduced RV compliance may play a role in the recovery of active atrial function after PPVI. Furthermore, it might be possible that early changes in RA function may differ between the 2 groups, whereas long-term remodeling may be similar. With the present data, any statement on a critical cutoff for RV dimensions that is associated with sufficient RA functional

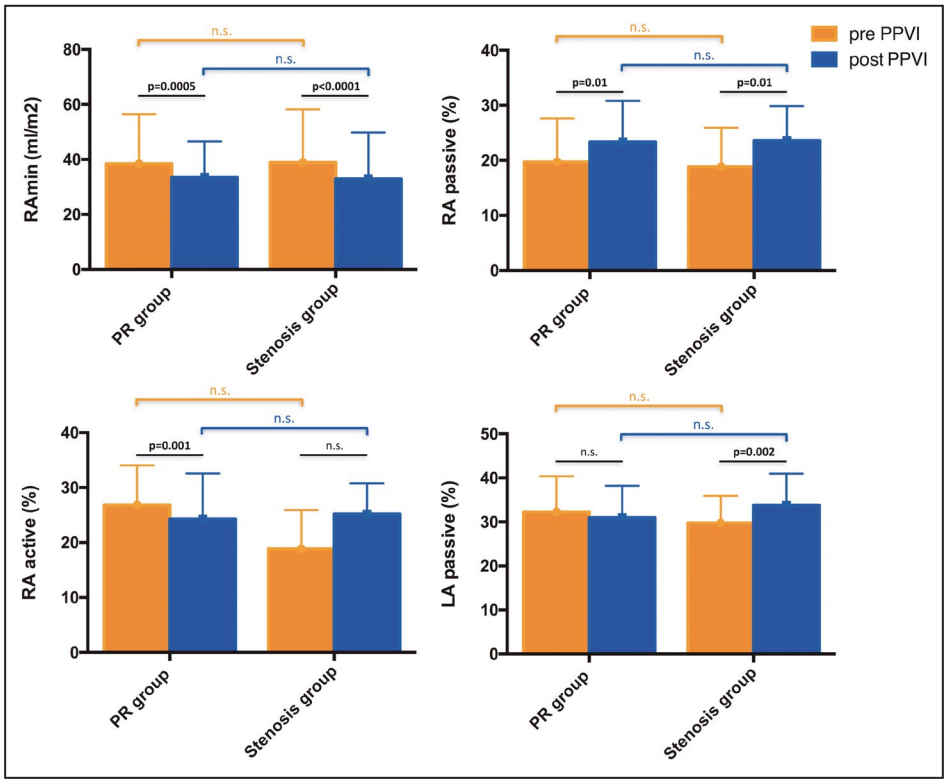

Figure 7. Graphs displaying changes of right atrial minimal volume (RAmin), right atrial (RA) and left atrial (LA) passive, and RA active emptying function before (orange) and after (blue) percutaneous pulmonary valve implantation (PPVI) in a matched subgroup analysis comparing patients with primary right ventricular (RV) pressure overload with patients affected by primary RV volume overload.
Data are presented as mean with 1 SD. n.s. indicates not significant.

recovery is not possible, but might be feasible in the future with a larger data set.

RA Physiology as Predictor for Improvement in Exercise Capacity or RV Function

Neither changes in RA volumes nor parameters of atrial emptying were able to predict an improvement in peak VO_2 or RVEF during the short-term after PPVI. These results suggest that assessment of atrial emptying properties may not help to predict short-term clinical improvements after PPVI, although long-term outcomes on adverse events are not yet available in our population. In contrast, significant predictors for better peak VO_2 after PPVI were lower baseline peak VO_2, lower baseline RVOT gradient, and the absolute change in RVOT gradient. Consequently, even if a high RVOT gradient can be effectively reduced by PPVI, exercise performance remains unchanged or even decreases. Notably, this finding is in contrast to a previous report in which a reduction in the RVOT gradient was the only independent predictor of improved peak oxygen uptake.[27] Although the reason for these contradictory results remains unclear (other factors such as underlying diagnoses, age at intervention, and PR severity may have an impact), both the extent of RV afterload and its absolute reduction occurring with PPVI seem to be more important modulators of exercise function than other clinical parameters including biventricular function.[28] Further research in this field is warranted, because adequate indication and timing of RVOT interventions are crucial in this patient population.

Study Limitations

A limitation of our study is that a comparison of atrial dimensions and function with an age- matched healthy control group was not possible. Therefore, conclusions about normalization of these parameters after PPVI cannot be made. The observed correlations should not be interpreted as causal relationships in view of the observational design of the study. Our analysis included patients with various congenital heart diagnoses who were referred for PPVI, whereas most of the existing data on atrial function in this population are based on repaired patients with TOF predominantly

Table 3. Binary Logistic Regression Analysis for the Outcome Measure Improved Peak VO_2 After PPVI

Parameter	OR	95% CI	*P* value
Age at PPVI, y	1.02	0.97–1.07	0.47
NYHA > class I	0.74	0.27–2.07	0.57
Peak VO_2, mL/min per kg	0.95	0.89–1.01	0.11
Peak VO_2 predicted, %	0.96	0.93–0.99	0.01*
RVOT gradient echocardiography, mm Hg	0.97	0.94–0.99	0.012*
TR > moderate, yes/no	0.96	0.32–2.86	0.94
RVEDP catheterization, mm Hg	1.01	0.87–1.16	0.94
RVEDVi, mL/m^2	1.02	1.00–1.05	0.05
RVESVi, mL/m^2	1.03	0.98–1.06	0.07
RVSVi, mL/m^2	1.01	0.98–1.05	0.46
RVEF, %	0.98	0.94–1.02	0.36
PR, %	1.01	0.97–1.04	0.80
LVEDVi, mL/m^2	1.00	0.97–1.03	0.95
LVESVi, mL/m^2	0.98	0.94–1.03	0.45
LVSVi, mL/m^2	1.02	0.97–1.07	0.39
LVEF, %	1.03	0.98–1.09	0.22
RA_{max}, mL/m^2	1.00	0.98–1.03	0.86
RA_{min}, mL/m^2	1.00	0.97–1.03	0.95
RA cyclic volume change, mL/m^2	1.01	0.95–1.09	0.72
RA passive emptying function, %	0.98	0.90–1.07	0.65
RA active emptying function, %	1.04	0.96–1.12	0.34
RA E/A	0.52	0.16–1.64	0.26
LA_{max}, mL/m^2	0.99	0.94–1.03	0.52
LA_{min}, mL/m^2	0.98	0.91–1.06	0.67
LA passive emptying function, %	1.01	0.94–1.09	0.79
LA active emptying function, %	0.99	0.91–1.08	0.81
Δ RVOT gradient echocardiography, mm Hg	0.97	0.94–0.99	0.007*
Δ RA_{max}, mL/m^2	0.99	0.92–1.05	0.64
Δ RA_{min}, mL/m^2	0.97	0.90–1.05	0.44
Δ RA passive emptying function, %	1.01	0.89–1.17	0.80
Δ RA active emptying function, %	1.06	0.94–1.20	0.32
Δ LA_{max}, mL/m^2	1.02	0.95–1.10	0.58
Δ LA_{min}, mL/m^2	1.04	0.91–1.18	0.59
Δ LA passive emptying function, %	1.00	0.91–1.11	0.95
Δ LA active emptying function, %	1.04	0.93–1.17	0.51

EDP indicates end-diastolic pressure; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; i, indexed to body surface area; LA, left atrial; LV, left ventricular; NYHA, New York Heart Association functional class; OR, odds ratio; PPVI, percutaneous pulmonary valve implantation; PR, pulmonary regurgitation; RA, right atrial; RV, right ventricular; RVOT, right ventricular outflow tract; SV, stroke volume; TR, tricuspid valve regurgitation; and VO_2, oxygen uptake.

*$P<0.05$.

Table 4. Binary Logistic Regression Analysis for the Outcome Measure Improved RVEF After PPVI

Parameter	OR	95% CI	*P* value
Age at PPVI, y	0.97	0.94–1.01	0.16
NYHA > class I	2.90	1.06–7.95	0.039*
Peak VO_2, mL/min per kg	1.00	0.95–1.05	0.95
Peak VO_2 predicted, %	0.99	0.96–1.01	0.33
RVOT gradient echocardiography, mm Hg	1.01	1.00–1.03	0.15
TR > moderate, yes/no	0.97	0.39–2.41	0.95
RVEDP catheterization, mm Hg	1.06	0.95–1.19	0.30
RVEDVi, mL/m^2	1.01	0.99–1.02	0.31
RVESVi, mL/m^2	1.05	1.02–1.08	0.002*
RVSVi, mL/m^2	0.94	0.90–0.97	0.001*
RVEF, %	0.88	0.83–0.93	0.0001*
PR, %	0.98	0.96–1.01	0.28
LVEDVi, mL/m^2	1.00	0.97–1.02	0.81
LVESVi, mL/m^2	1.02	0.98–1.07	0.26
LVSVi, mL/m^2	0.97	0.93–1.01	0.13
LVEF, %	0.95	0.90–1.00	0.036*
RA_{max}, mL/m^2	1.01	0.99–1.03	0.43
RA_{min}, mL/m^2	1.02	0.99–1.05	0.24
RA cyclic volume change, mL/m^2	0.99	0.93–1.05	0.68
RA passive emptying function, %	0.98	0.91–1.05	0.52
RA active emptying function, %	0.98	0.92–1.04	0.45
RA E/A	0.79	0.49–1.27	0.33
LA_{max}, mL/m^2	0.98	0.94–1.02	0.24
LA_{min}, mL/m^2	0.99	0.93–1.04	0.62
LA passive emptying function, %	1.02	0.95–1.09	0.68
LA active emptying function, %	0.98	0.91–1.05	0.55
Δ RVOT gradient echocardiography, mm Hg	1.01	0.99–1.03	0.16
Δ RA_{max}, mL/m^2	1.01	0.96–1.07	0.71
Δ RA_{min}, mL/m^2	0.97	0.91–1.04	0.34
Δ RA passive emptying function, %	1.06	0.96–1.18	0.23
Δ RA active emptying function, %	1.08	0.98–1.19	0.13
Δ LA_{max}, mL/m^2	1.04	0.97–1.11	0.28
Δ LA_{min}, mL/m^2	0.99	0.89–1.10	0.84
Δ LA passive emptying function, %	1.06	0.98–1.15	0.14
Δ LA active emptying function, %	1.02	0.93–1.13	0.66

EDP indicates end-diastolic pressure; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; i, indexed to body surface area; LA, left atrial; LV, left ventricular; NYHA, New York Heart Association functional class; OR, odds ratio; PPVI, percutaneous pulmonary valve implantation; PR, pulmonary regurgitation; RA, right atrial; RV, right ventricular; RVOT, right ventricular outflow tract; SV, stroke volume; TR, tricuspid valve regurgitation; and VO_2, oxygen uptake.

*$P<0.05$.

affected by PR. Furthermore, as the number of patients with pure volume overload (PR >20% and peak RVOT gradient <50 mm Hg) was low, the subgroup analysis also included patients with a mixed lesion (PR >20% and peak RVOT gradient >50 mm Hg).[25] Differentiation between intrinsic atrial dysfunction and

impaired ventricular filling was not possible in the current study. Although assessment of late gadolinium enhancement would provide further information about the potential relationship between RV myocardial fibrosis and RA function, this technique was not part of the routine CMR imaging protocol. Finally, analysis of atrial emptying function was not possible in all patients, and because of the short-term follow-up of 6 months after PPVI, the long-term changes and prognostic relevance of atrial volumes and function remain unknown.

CONCLUSIONS

In patients with RVOT dysfunction and various degrees of pressure and volume overload, parameters of RA emptying assessed by CMR imaging correlated with invasive RV end-diastolic pressures and impaired RA emptying was associated with reduced exercise performance. Passive RA emptying function improved, and active RA emptying decreased after PPVI. Patients with primary pressure overload showed more favorable changes in RA and LA emptying than patients with predominant volume overload. None of the RA emptying parameters was predictive for recovery of exercise function or RV pump function short term after PPVI.

ARTICLE INFORMATION

Received March 19, 2021; accepted August 23, 2021.

Affiliations

Department of Congenital Heart Disease and Pediatric Cardiology, German Heart Centre Munich, Technical University of Munich, Munich, Germany (H.L., D.B., N.S., H.S., A.H., S.G., D.T., C.M., P.E., A.E., O.T.); and German Centre for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance, Munich, Germany (P.E., O.T.).

Acknowledgment

Open access funding enabled and organized by ProjektDEAL.

Sources of Funding

None.

Disclosures

Dr Ewert reports support from Medtronic and Edwards Lifescience outside the submitted work. Dr Eicken reports personal fees from Medtronic during the conduct of the study. Dr Tutarel reports personal fees from Janssen outside the submitted work. The remaining authors have no disclosures to report.

REFERENCES

1. Valente AM, Gauvreau K, Assenza GE, Babu-Narayan SV, Schreier J, Gatzoulis MA, Groenink M, Inuzuka R, Kilner PJ, Koyak Z, et al. Contemporary predictors of death and sustained ventricular tachycardia in patients with repaired tetralogy of fallot enrolled in the indicator cohort. *Heart*. 2014;100:247–253. doi: 10.1136/heartjnl-2013-304958
2. Bonello B, Kempny A, Uebing A, Li W, Kilner PJ, Diller GP, Pennell DJ, Shore DF, Ernst S, Gatzoulis MA, et al. Right atrial area and right ventricular outflow tract akinetic length predict sustained tachyarrhythmia in repaired tetralogy of fallot. *Int J Cardiol*. 2013;168:3280–3286. doi: 10.1016/j.ijcard.2013.04.048
3. Ait Ali L, Lurz P, Ripoli A, Rossi G, Kister T, Aquaro GD, Passino C, Bonhoeffer P, Festa P. Implications of atrial volumes in surgical corrected tetralogy of fallot on clinical adverse events. *Int J Cardiol*. 2019;283:107–111. doi: 10.1016/j.ijcard.2019.02.018
4. Friedberg MK, Fernandes FP, Roche SL, Grosse-Wortmann L, Manlhiot C, Fackoury C, Slorach C, McCrindle BW, Mertens L, Kantor PF. Impaired right and left ventricular diastolic myocardial mechanics and filling in asymptomatic children and adolescents after repair of tetralogy of fallot. *Eur Heart J Cardiovasc Imaging*. 2012;13:905–913. doi: 10.1093/ehjci/jes067
5. Tretter JT, Friedberg MK, Wald RM, McElhinney DB. Defining and refining indications for transcatheter pulmonary valve replacement in patients with repaired tetralogy of fallot: contributions from anatomical and functional imaging. *Int J Cardiol*. 2016;221:916–925. doi: 10.1016/j.ijcard.2016.07.120
6. Apitz C, Latus H, Binder W, Uebing A, Seeger A, Bretschneider C, Sieverding L, Hofbeck M. Impact of restrictive physiology on intrinsic diastolic right ventricular function and lusitropy in children and adolescents after repair of tetralogy of fallot. *Heart*. 2010;96:1837–1841. doi: 10.1136/hrt.2010.203190
7. Muller J, Engelhardt A, Fratz S, Eicken A, Ewert P, Hager A. Improved exercise performance and quality of life after percutaneous pulmonary valve implantation. *Int J Cardiol*. 2014;173:388–392. doi: 10.1016/j.ijcard.2014.03.002
8. Tanase D, Ewert P, Georgiev S, Meierhofer C, Pabst von Ohain J, McElhinney DB, Hager A, Kuhn A, Eicken A. Tricuspid regurgitation does not impact right ventricular remodeling after percutaneous pulmonary valve implantation. *JACC Cardiovasc Interv*. 2017;10:701–708. doi: 10.1016/j.jcin.2017.01.036
9. Luijnenburg SE, Peters RE, van der Geest RJ, Moelker A, Roos-Hesselink JW, de Rijke YB, Mulder BJ, Vliegen HW, Helbing WA. Abnormal right atrial and right ventricular diastolic function relate to impaired clinical condition in patients operated for tetralogy of fallot. *Int J Cardiol*. 2013;167:833–839. doi: 10.1016/j.ijcard.2012.02.011
10. Wohlmuth C, Kellenberger CJ, Voser EM, Burkhardt BE, Buechel ER. Cardiac function after repair of tetralogy of fallot: how are the atria performing? Pilot study by cardiac magnetic resonance imaging. *Pediatr Cardiol*. 2015;36:96–105. doi: 10.1007/s00246-014-0970-y
11. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, Badano L, Zamorano JL. Scientific document committee of the european association of cardiovascular I. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the european association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging*. 2013;14:611–644. doi: 10.1093/ehjci/jet105
12. Kutty S, Valente AM, White MT, Hickey K, Danford DA, Powell AJ, Geva T. Usefulness of pulmonary arterial end-diastolic forward flow late after tetralogy of fallot repair to predict a "restrictive" right ventricle. *Am J Cardiol*. 2018;121:1380–1386. doi: 10.1016/j.amjcard.2018.02.025
13. Egbe AC, Bonnichsen C, Reddy YNV, Anderson JH, Borlaug BA. Pathophysiologic and prognostic implications of right atrial hypertension in adults with tetralogy of fallot. *J Am Heart Assoc*. 2019;8:e014148. doi: 10.1161/JAHA.119.014148
14. Westenberg JJ. CMR for assessment of diastolic function. *Curr Cardiovasc Imaging Rep*. 2011;4:149–158. doi: 10.1007/s12410-011-9070-z
15. Riesenkampff E, Mengelkamp L, Mueller M, Kropf S, Abdul-Khaliq H, Sarikouch S, Beerbaum P, Hetzer R, Steendijk P, Berger F, et al. Integrated analysis of atrioventricular interactions in tetralogy of fallot. *Am J Physiol Heart Circ Physiol*. 2010;299:H364–H371. doi: 10.1152/ajpheart.00264.2010
16. Pijuan-Domenech A, Pineda V, Castro MA, Sureda-Barbosa C, Ribera A, Cruz LM, Ferreira-Gonzalez I, Dos-Subirà L, Subirana-Domènech T, Garcia-Dorado D, et al. "Pulmonary valve replacement diminishes the presence of restrictive physiology and reduces atrial volumes": a prospective study in tetralogy of fallot patients. *Int J Cardiol*. 2014;177:261–265. doi: 10.1016/j.ijcard.2014.09.009
17. Sohns JM, Rosenberg C, Zapf A, Unterberg-Buchwald C, Staab W, Schuster A, Kowallick JT, Hösch O, Nguyen TT, Fasshauer M, et al. Right atrial volume is increased in corrected tetralogy of fallot and correlates with the incidence of supraventricular arrhythmia: a CMR study. *Pediatr Cardiol*. 2015;36:1239–1247. doi: 10.1007/s00246-015-1152-2
18. Ait AL, Marrone C, Salvadori S, Federici D, Pak V, Arcieri L, Passino C, Santoro G, Festa P. Impact of right atrium dimension on adverse

outcome after pulmonary valve replacement in repaired tetralogy of fallot patients. *Int J Cardiovasc Imaging*. 2020;36:1973–1982. doi: 10.1007/s10554-020-01891-9

19. Romeih S, Kroft LJ, Bokenkamp R, Schalij MJ, Grotenhuis H, Hazekamp MG, Groenink M, de Roos A, Blom NA. Delayed improvement of right ventricular diastolic function and regression of right ventricular mass after percutaneous pulmonary valve implantation in patients with congenital heart disease. *Am Heart J*. 2009;158:40–46. doi: 10.1016/j.ahj.2009.04.023
20. Lunze FI, Hasan BS, Gauvreau K, Brown DW, Colan SD, McElhinney DB. Progressive intermediate-term improvement in ventricular and atrioventricular interaction after transcatheter pulmonary valve replacement in patients with right ventricular outflow tract obstruction. *Am Heart J*. 2016;179:87–98. doi: 10.1016/j.ahj.2016.05.011
21. Chowdhury SM, Hijazi ZM, Rhodes JF, Kar S, Makkar R, Mullen M, Cao QL, Mandinov L, Buckley J, Pietris NP, et al. Changes in speckle tracking echocardiography measures of ventricular function after percutaneous implantation of the edwards sapien transcatheter heart valve in the pulmonary position. *Echocardiography*. 2015;32:461–469. doi: 10.1111/echo.12700
22. Frigiola A, Giardini A, Taylor A, Tsang V, Derrick G, Khambadkone S, Walker F, Cullen S, Bonhoeffer P, Marek J. Echocardiographic assessment of diastolic biventricular properties in patients operated for severe pulmonary regurgitation and association with exercise capacity. *Eur Heart J Cardiovasc Imaging*. 2012;13:697–702. doi: 10.1093/ehjci/jes002
23. Jones TK, Rome JJ, Armstrong AK, Berger F, Hellenbrand WE, Cabalka AK, Benson LN, Balzer DT, Cheatham JP, Eicken A, et al. Transcatheter pulmonary valve replacement reduces tricuspid regurgitation in patients with right ventricular volume/pressure overload. *J Am Coll Cardiol*. 2016;68:1525–1535. doi: 10.1016/j.jacc.2016.07.734
24. Martin-Garcia AC, Dimopoulos K, Boutsikou M, Martin-Garcia A, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Babu-Narayan SV, Sanchez PL, et al. Tricuspid regurgitation severity after atrial septal defect closure or pulmonic valve replacement. *Heart*. 2019;106:455–461. doi: 10.1136/heartjnl-2019-315287
25. Lurz P, Nordmeyer J, Giardini A, Khambadkone S, Muthurangu V, Schievano S, Thambo JB, Walker F, Cullen S, Derrick G, et al. Early versus late functional outcome after successful percutaneous pulmonary valve implantation: are the acute effects of altered right ventricular loading all we can expect? *J Am Coll Cardiol*. 2011;57:724–731. doi: 10.1016/j.jacc.2010.07.056
26. Harrild DM, Marcus E, Hasan B, Alexander ME, Powell AJ, Geva T, McElhinney DB. Impact of transcatheter pulmonary valve replacement on biventricular strain and synchrony assessed by cardiac magnetic resonance feature tracking. *Circ Cardiovasc Interv*. 2013;6:680–687. doi: 10.1161/CIRCINTERVENTIONS.113.000690
27. Lurz P, Giardini A, Taylor AM, Nordmeyer J, Muthurangu V, Odendaal D, Mist B, Khambadkone S, Schievano S, Bonhoeffer P, et al. Effect of altering pathologic right ventricular loading conditions by percutaneous pulmonary valve implantation on exercise capacity. *Am J Cardiol*. 2010;105:721–726. doi: 10.1016/j.amjcard.2009.10.054
28. Chowdhury SM, Hijazi ZM, Fahey JT, Rhodes JF, Kar S, Makkar R, Mullen M, Cao QL, Shirali GS. Speckle-tracking echocardiographic measures of right ventricular function correlate with improvement in exercise function after percutaneous pulmonary valve implantation. *J Am Soc Echocardiogr*. 2015;28:1036–1044. doi: 10.1016/j.echo.2015.05.010